## REMARKS

### Amendments to the Claims

Claims 10 has been amended to delete the term "solvate". Claims 12-13 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 14-18 have been amended. Support for the claims are found, *e.g.*, at pages 16-19, page 25, lines 18-22, page 27, lines 29-32 and pages 28-31. Claims 10-11 and 14-24 are pending in this application. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### Written Description Requirement Rejection Should be Withdrawn

Claims 12 and 13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action states that there is no support in the specification for administrations of thalidomide in combination with the recited second agents for treating idiopathic pulmonary fibrosis (Page 3 of Office Action).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claims 12-13 have been canceled without prejudice. Thus, the rejection is moot in view of the amendment.

### The Claimed Invention Meets Enablement Requirements

Claims 10-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Office Action states that the specification, while being enabling for administration of thalidomide or a pharmaceutically acceptable salt or stereoisomer thereof, does not reasonably provide enablement for a solvate of thalidomide (Pages 3-5 of Office Action).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claim 10 has been amended by deleting solvate of thalidomide. Thus, the rejection is moot in view of the amendment.

Further, the Office Action states that the specification does not reasonably provide enablement for treating idiopathic pulmonary fibrosis in such a way that one skilled in the art can make and use the invention (Pages 5-9 of Office Action). Applicant respectfully traverses the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir.

1988)). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (Manual of Patent Examining Procedure ("MPEP") §2164.04, *citing In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Applicant respectfully submits that the specification adequately enables the pending claims, as amended. Specifically, the specification discloses the methods of treating idiopathic pulmonary fibrosis (IPF) by administering thalidomide to patients, including doses, modes of administration and dosage forms of thalidomide (*e.g.*, pages 16-19, page 25, lines 18-22, page 27, lines 29-32 and pages 28-31). Thus, one skilled in the art would have been able to practice the claimed invention by administering the specified amount of thalidomide using the specified routes of administration to the specified patients, in accordance with the explicit teachings of the present application.

The specification clearly describes that IPF is a disease associated with or characterized by undesired angiogenesis (page 17, line 18 to page 18, line 12). The specification also discloses that thalidomide is an antiangiogenic agent that can suppress tumor necrosis factor α (TNF-α) and interleukin 12 (IL-12) production (page 5, lines 1-2). The inhibition of TNF-α production is disclosed on page 36, Example 5.

Thus, from the description of the specification, one skilled in the art would have been able to appreciate that the inhibition of angiogenesis by administration of thalidomide would lead to the treatment of IPF. The specification provides a sufficient guidance as to treating IPF by administering an effective amount of thalidomide.

Nonetheless, the Office Action states that there is no evidence of record that IPF is caused by angiogenesis, and one would not believe that thalidomide would have any efficacy in the treatment of this disease. (Page 9 of the Office Action). Applicant respectfully disagrees.

Applicant herewith submits several articles that were published after the filing date of this application, to support the effect of thalidomide in treating IPF[1]. For example, Allen *et al.*, Zisman *et al.*, Tabata *et al.*, Ye *et al.* and Horton *et al.* describe that targeting angiogenesis and TNF-α were effective therapeutic strategy in IPF, that thalidomide had antiangiogenic effect and TNF-α inhibition, and that thalidomide was effective in treating patients with IPF. Therefore, the evidence provided herein establishes the efficacy of thalidomide in treating IPF. These publications evidence that a skilled in the art can use and

[1] Attached hereto with supplemental IDS and list of references cited. Applicant requests that all these references be made of record in the file history of the application and request the Examiner execute the 1449 form enclosed.

practice the claimed invention for treating IPF using thalidomide, based on the disclosure of the specification. As such, Applicant respectfully submits that the treatment of IPF as claimed is adequately enabled in this application, and requests that the rejection be withdrawn.

Further, Applicant notes that the Office Action cites two articles in an attempt to negate enablement for the claimed invention, alleging that administrations of other agents to IPF patients resulted in no good results. (Pages 7-8). Applicant respectfully submits that such an alleged teaching does not establish a reasonable basis to question the enablement of the instant claims. Although Applicant notes that the cited articles disclosed poor results of several drugs against IPF in certain studies, the present claims are distinct from those articles, because the instant claims recite the use of different drug thalidomide. Indeed, the articles teach away from the invention, because they focus on different drugs. Applicant respectfully reminds the PTO that the fact that a reference teaches away from a claimed invention is not a proper basis for an enablement rejection. As the Federal Circuit explained, although the question of whether or not a reference teaches away from a claimed invention is relevant in determining obviousness, "[it is] not the primary [question] bearing on enablement." (emphasis added). (*Singh v. Brake*, 317 F.3d 1334, 1346, 65 U.S.P.Q.2d. 1641 (Fed. Cir. 2003), the Federal Circuit concluded that the appellant "apparently confused the criteria for proving obviousness with those for demonstrating that a disclosure is nonenabling"). Thus, Applicant respectfully submits that such articles which teach away from the claimed invention can not be the basis of a rejection under §112 because it does not establish a reasonable basis to question the enablement of the instant claims.

Further, the PTO's contention that current therapies were not effective in IPF is not relevant for purposes of satisfying the enablement requirement. As the Examiner is well aware, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." (MPEP 2164.02, *quoting Gould v. Quigg*, 822 F.2d 1074, 1078, 2 U.S.P.Q. 2d 1302 (Fed. Cir. 1987), *quoting In re Chilowsky*, 229 F.2d 457, 461, 108 U.S.P.Q. 321 (CCPA 1956)). Applicant respectfully submits that the references submitted herewith show that thalidomide is effective in treating IPF.

As to the working examples disclosed in the specification, the Office Action alleges that they are limited to demonstrating the inhibition of TNF-α production of thalidomide, but there are no *in vitro* or *in vivo* experimental models of any diseases described, including IPF (Office Action, page 8). Applicant respectfully submits that contrary to the allegations, the

data reasonably correlates with the claimed invention. Example 5 of the specification discloses the inhibition of TNF-α production by thalidomide. (Specification, page 36). "[A]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." *In re Brana*, at 1566; MPEP §2164.02. "A rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

Further, the specification clearly describes that IPF is associated with angiogenesis and that inhibitions of angiogenesis and TNF-α production would lead to treatment of IPF (page 5, lines 1-2, and pages 17-18). (*See also* MPEP §2164.04, *citing in re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367 (CCPA 1971) (A specification disclosure is "presumptively accurate") (emphasis added))). Thus, Applicant respectfully submits that the example in the specification, in effect, constitutes working example for the claimed invention. *In re Brana*, at 1566; MPEP § 2164.02. The Office Action has not provided with any evidence that the examples disclosed in the specification do not correlate with the treatment of IPF. Applicant respectfully reminds the Examiner that "[s]ince the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must...give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required..." (*Id., citing Cross v. Iizuka*, at 1050 (Fed. Cir. 1985)).

Furthermore, Applicant respectfully notes that as well settled, proof of clinical efficacy and human data are not required for purposes of satisfying the enablement requirement. For example, in *In re Brana*, in a manner similar to the Examiner in the present case, the PTO alleged that animal testing was not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Court rejected this argument and stated that "[t]he Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." (51 F.2d at 1567). Moreover, the Court stated that "Title 35 does not demand that such human testing occur within the confines of the Patent and Trademark Office Proceedings." (*Id., citing Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d (B.N.A.) 115 (Fed. Cir. 1994); *see also MPEP §2164* ("[t]he applicant need not demonstrate that the invention is completely safe.")).

Nonetheless, the Office Action alleges that "[t]he specification provides no direction or guidance for determining the particular administration regimens (e.g. dosages, timing,

administration routes, etc.) necessary to treat IPF, particularly in humans."[2] (Office Action, page 8). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the specification does provide sufficient guidance to enable one of skill in the art to practice the claimed invention. Specifically, doses, dosage forms and routes of administration of thalidomide are provided in the instant specification (*e.g.*, page 25, lines 18-22, page 27, lines 29-32 and pages 28-31). Applicant respectfully submits that the Examiner appears to be objecting to a screening step. Indeed, the determination by a physician as to whether a compound is effective in treating a disorder is routine and is performed by physicians for every pharmaceutical. With regard to screening for effective dosages for the treatment of a disorder in a human, the Board of Patent Appeals and Interferences in *Ex parte Skuballa* stated:

> While some experimentation may be required to determine optimum dosages...such experimentation is not considered undue...We are satisfied that the skilled worker in this art could readily optimize effective dosages and administration regimens... As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures.

(12 U.S.P.Q.2d 1570 (Bd. Pat. App. & Interf. 1989)) (emphasis added).

Thus, to the extent the PTO is basing the rejection under 35 U.S.C. §112 on the need for screening, Applicant respectfully submits that such a rejection is improper. One skilled in the art would have been able to practice the claimed invention by administering the specified amount of thalidomide using the specified routes of administration to patients having IPF, as provided in the instant specification.

In sum, Applicant respectfully submits that the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention, and that to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

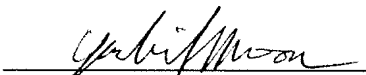
[2] As discussed, *supra*, the lack of clinical or human data is not a proper basis for an enablement rejection.

## Conclusion

Applicant respectfully requests that the above amendments and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: December 23, 2008



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